Attorney Docket No.:
BAYU-0002 WO/US (208614.00088)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Pinney, Kevin G., et al.

Serial No.: 10/594,105

Filed: March 28, 2005

For: **NOVEL SEROTONIN REUPTAKE INHIBITORS**

Group No.: 1624

Examiner: Leeser, Erich A.

Mail Stop Amendment
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT UNDER 37 C.F.R. §1.111

The Examiner contacted the Applicant's Representative by telephone on January 12, 2010, requesting that the response filed December 8, 2009 be resubmitted due to an apparent error in the placement of the mark-up indicating which structures should be removed in the amended claims. Therefore, please disregard the previously filed amendment, and amend the above-identified patent application as follows:

IN THE CLAIMS:

1. (Withdrawn) A serotonin reuptake inhibitor comprising:

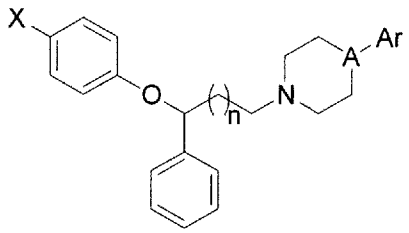
a first part, wherein the first part comprises a moiety with antidepressant properties and having an affinity for the serotonin reuptake transporter (SERT); and

a second part, wherein the second part comprises a moiety having an affinity to serotonin (5-HT) receptors, and wherein the second part is coupled to the first part.

2. (Withdrawn) The serotonin reuptake inhibitor of claim 1, wherein the 5-HT is 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, or 5-HT_3.

3. (Withdrawn) The serotonin reuptake inhibitor of claim 1, wherein the 5-HT is 5-HT_{2A}.

4. (Currently Amended) A serotonin reuptake inhibitor having the general formula:



,

~~wherein X is F or CF_3;~~

~~n is 0 or 1;~~

~~A is N or C; and~~

~~Ar is an aryl moiety; and salt thereof.~~

wherein when X = F; n = 0; and A = N:

Ar is an aryl moiety, or salt thereof, excluding 3-chlorophenyl, 2-methoxyphenyl, and 3-trifluoromethylphenyl;

wherein when X = F; n = 0; and A = C:

Ar is an aryl moiety, or salt thereof;

wherein when X = F; n = 1; and A = N or C:

Ar is an aryl moiety, or salt thereof;

wherein when X = CF_3; n = 0; and A = N or C:

Ar is an aryl moiety, or salt thereof;

wherein when X = CF_3; n = 1; and A = N:

Ar is a substituted aryl moiety, or salt thereof, excluding benzo[d]isothiazole, 2-methoxyphenyl, 4-fluorophenyl, 4-methoxyphenyl, 2-pyrimidyl, 2-chlorophenyl, 4-chlorophenyl, 2-pyridyl, and 4-nitrophenyl; and

wherein X = CF_3; n = 1; and A = C:

Ar is an aryl moiety, or salt thereof.

5. (Withdrawn) A serotonin reuptake inhibitor comprising a bi-functional organic molecule combining serotonin (5-HT) receptor antagonism and serotonin reuptake inhibition into one molecular entity.

6. (Withdrawn) The serotonin reuptake inhibitor of claim 5, wherein the 5-HT is 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, or 5-HT_3.

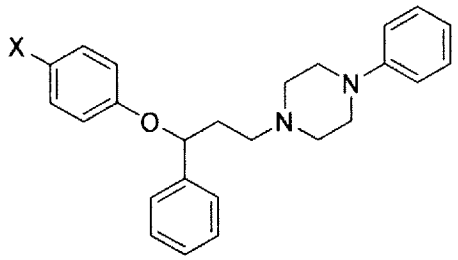
7. (Withdrawn) The serotonin reuptake inhibitor of claim 5, wherein the 5-HT is 5-HT_{2A}.

8. (Withdrawn) A serotonin reuptake inhibitor comprising a structural homologue of an antidepressant serotonin-selective reuptake inhibitor (SSRI) capable of inhibiting serotonin reuptake transporter (SERT) coupled to a piperazine or piperidine moiety being antagonistic to a serotonin (5-HT) receptor.

9. (Withdrawn) The serotonin reuptake inhibitor of claim 8, wherein the 5-HT is 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, or 5-HT_3.

10. (Withdrawn) The serotonin reuptake inhibitor of claim 8, wherein the 5-HT is 5-HT_{2A}.

11. (Currently Amended) A serotonin reuptake inhibitor having the general formula:

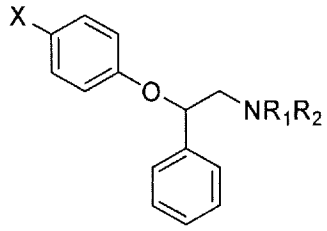


,

wherein X is F ~~or CF_3~~; and

salt thereof.

12. (Currently Amended) A serotonin reuptake inhibitor having the general formula:



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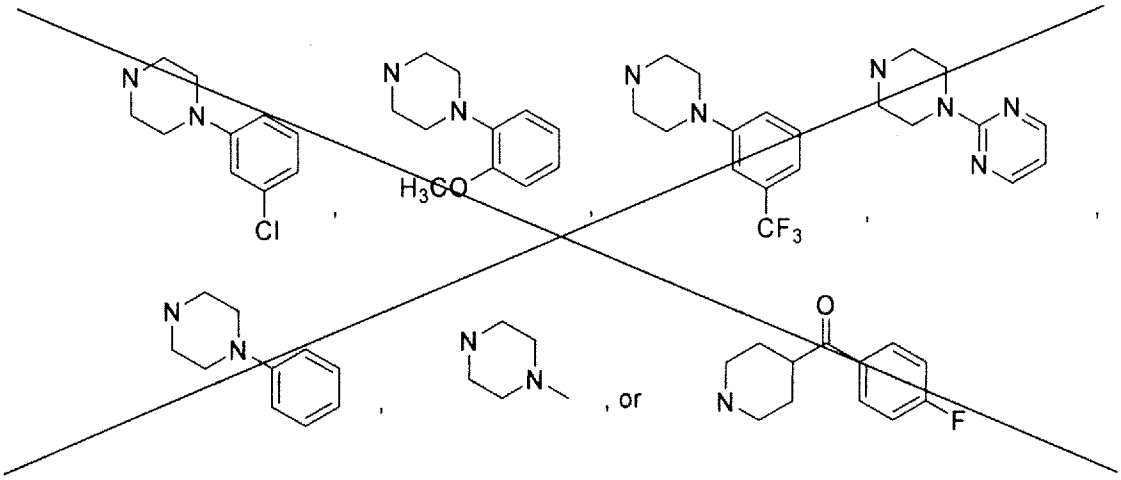
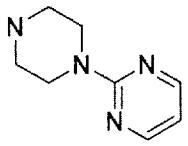
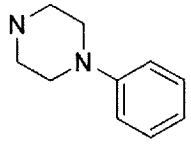
wherein X is F ~~or CF_3~~;

wherein NR_1R_2 is:



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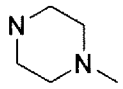
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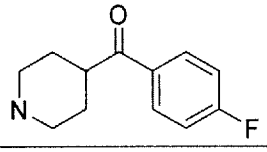
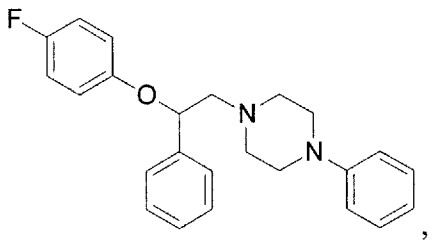

; and

salt thereof.

13. (Cancelled)

14. (Currently Amended) A serotonin reuptake inhibitor having the formula: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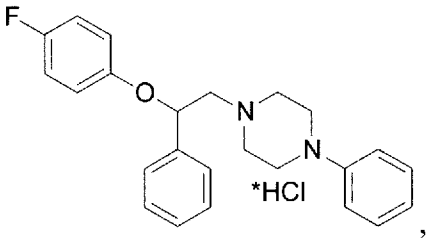
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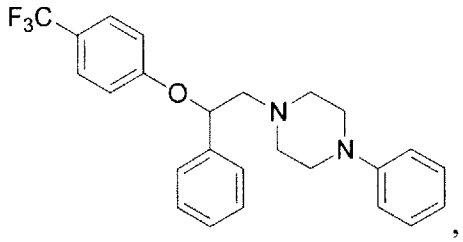
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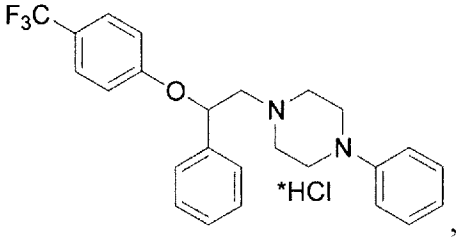
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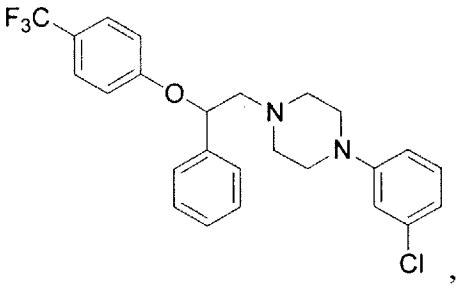
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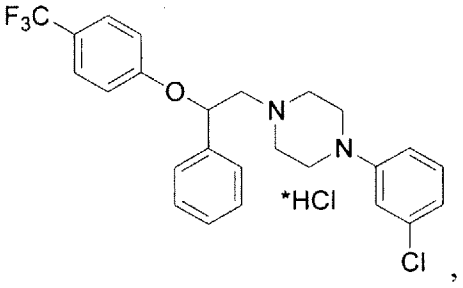
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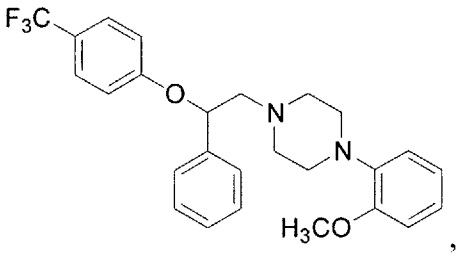
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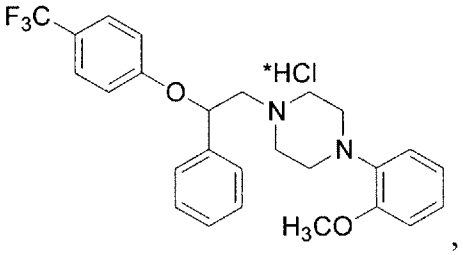
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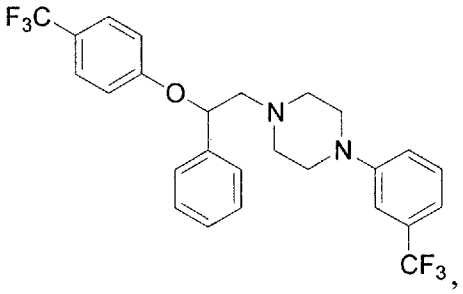
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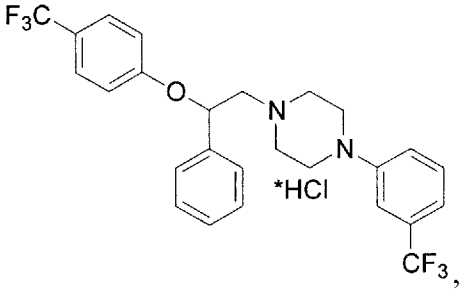
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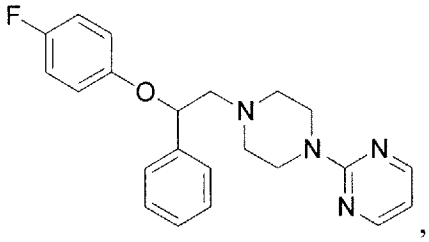
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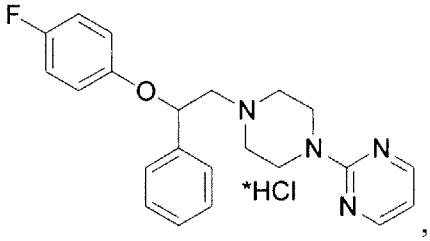
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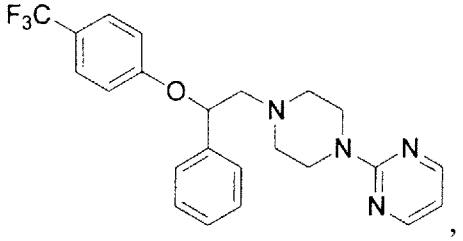
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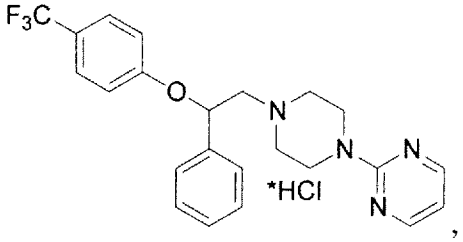
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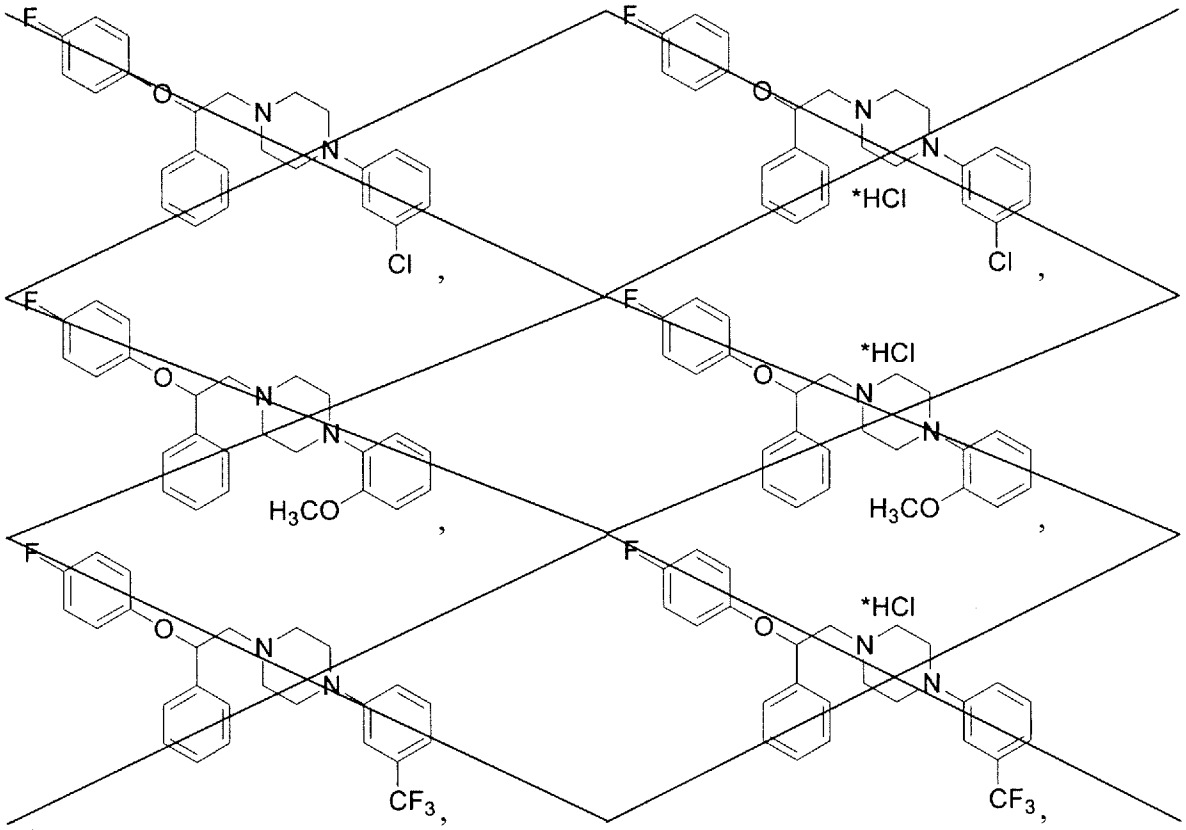

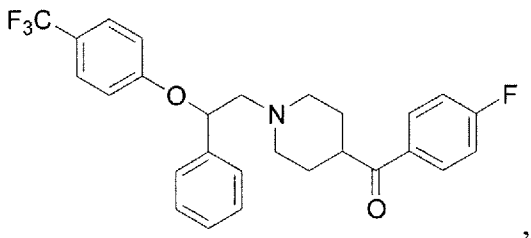

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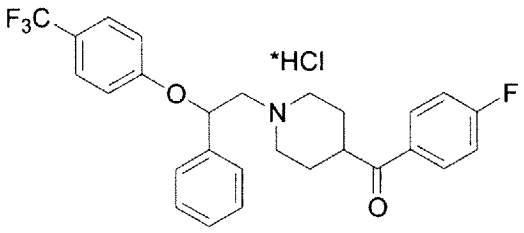

.

15. (Withdrawn) A method for treating depression in a patient, comprising:

administering the serotonin reuptake inhibitor of claim 1.

16. (Withdrawn) A method for treating depression in a patient, comprising:

administering the serotonin reuptake inhibitor of claim 4.

17. (Withdrawn) A method for treating depression in a patient, comprising:

administering the serotonin reuptake inhibitor of claim 5.

18. (Withdrawn) A method for treating depression in a patient, comprising:

administering the serotonin reuptake inhibitor of claim 8.

19. (Withdrawn) A method for treating depression in a patient, comprising:

administering the serotonin reuptake inhibitor of claim 12.

20. (Withdrawn) A pharmaceutical formulation for the treatment of depression in a patient, comprising:

a pharmaceutically effective amount of the serotonin reuptake inhibitor of claim 1.

21. (Original) A pharmaceutical formulation for the treatment of depression in a patient, comprising:

a pharmaceutically effective amount of the serotonin reuptake inhibitor of claim 4.

22. (Withdrawn) A pharmaceutical formulation for the treatment of depression in a patient, comprising:

a pharmaceutically effective amount of the serotonin reuptake inhibitor of claim 5.

23. (Withdrawn) A pharmaceutical formulation for the treatment of depression in a patient, comprising:

a pharmaceutically effective amount of the serotonin reuptake inhibitor of claim 8.

24. (Original) A pharmaceutical formulation for the treatment of depression in a patient, comprising:

a pharmaceutically effective amount of the serotonin reuptake inhibitor of claim 12.

REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Office Action, and respectfully request reconsideration of this Application in view of the above amendments and the following remarks.

Claims 1-24 are pending in this application. Claims 1-3, 5-10, 15-20, and 22-23, have been withdrawn as being drawn to non-elected subject matter.

Claim 4 has been amended to more specifically characterize an embodiment of the present invention.

Claim 11 has been amended to recite a specific functional group in an embodiment of the present invention.

Claim 12 has been amended to recite specific structures in an embodiment of the present invention.

Claim 13 has been cancelled.

Claim 14 has been amended to recite specific structures in an embodiment of the present invention.

I. CLAIM REJECTIONS UNDER 35 USC §102

A. The Examiner has rejected Claims 4, 11, and 13, under 35 U.S.C. 102(b) as being anticipated by Jakobsen et al. EP 576766 ("the Jakobsen Reference"). The Examiner states that the Jakobsen Reference teaches the preparation of (hetero)arylpropanolamine derivatives, specifically 1-phenyl-4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-ethanedioate piperazine.

It is a well-known tenet of patent law that, in order to anticipate a claim, a reference must teach every element of the claim (see MPEP 2131). In the present case, the Jakobsen Reference does not teach every element of Claims 4 and 11, as amended. Claim 13 has been cancelled.

Specifically, Claim 4, as amended, excludes the compounds of the Jakobsen Reference because Ar may not be unsubstituted when A=N, n=1, and X=CF_3.

Claim 11, as amended, and recites that X=F, which excludes the compounds of the Jakobsen Reference.

Therefore, Claims 4, and 11, as amended, recite distinct compounds from the compounds of the Jakobsen Reference, and cannot be anticipated by the reference. Applicants respectfully request that the rejection be withdrawn.

B. The Examiner has rejected Claims 4, 12, 14, 21, and 24, under 35 U.S.C. 102(b) over Dorsey et al. *Bioorganic & Medicinal Chemistry* 12:1483-91, 2004 ("the Dorsey Reference"). The Examiner states that this reference teaches 2-(4-fluorophenoxy)-2-phenyl-ethyl piperazines which anticipate the current claims.

As described above, it is well known that, in order to anticipate a claim, a reference must teach every element of the claim (see MPEP 2131). In the present case, the Dorsey Reference does not teach every element of Claims 4, 12, 14, 21, and 24, as amended.

Claim 4, as amended, excludes the situation wherein X=F, n=0, A is N, and Ar = 3-chlorophenyl, 2-methoxyphenyl, and 3-trifluoromethylphenyl.

Claim 12, as amended, excludes 3-chlorophenyl, 2-methoxyphenyl, and 3-trifluoromethylphenyl, when X=F.

Claim 14, as amended, excludes 3-chlorophenyl, 2-methoxyphenyl, and 3-trifluoromethylphenyl, when X=F.

Claims 21 and 21 are dependent claims, and the rejection will be overcome by amendments to Claims 4 and 12.

II. CLAIM REJECTIONS UNDER 35 USC §103

A. The Examiner has rejected Claims 4, 14, 21, and 24, under 35 USC 103, over Oficialdegui, et al. *Farmaco* 55(5):345-353, 2000 ("the Oficialdegui Reference"). The Examiner states that this reference teaches 3-[(4-aryl)piperazin-1-yl]-1-arylpropane derivatives, which differ only in that the claimed compounds lack the methylated phenyl of the compound of the reference.

As the Examiner has acknowledged, the compounds of the Oficialdegui Reference include a methylated phenyl which is lacking in the currently claimed compounds. In addition, Claims 4 and 21, as amended, exclude 2-methoxyphenyl and 4-methoxyphenyl in cases where $X=CF_3$, n=1, and A=N. Claims 14 and 24 differ in that they have a phenyl group, while the reference teaches a methoxyphenyl group. Therefore, there are clear differences in one or more functional groups of each claimed molecule when compared with the teachings of the reference.

It is well known in pharmacology that changes to a single functional group in a molecule can have a dramatic effect on the affinity of that molecule for a receptor, and the ability of that molecule to activate a receptor. Therefore, it would have been well understood by one of skill in the art that a hypothetical change to a lead compound would not enable one to predict the properties of the resulting molecule. Because there is no way to predict the effect of different functional groups in a new molecule, one of skill in the art would not have been able to select the particular lead compounds or make the changes to functional groups disclosed in the present application in order to solve the problem of providing an improved serotonin reuptake inhibitor. Determination of obviousness for claims relating to new pharmacologic compounds is addressed in a series of decisions by the United States Supreme Court and the U.S. Court of Appeals.

The United States Supreme Court has held in *KSR International vs. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385 (200 7), that "(w)hen there is design need or market pressure to solve a problem and there are a **finite number of identified, predictable solutions**, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill

and common sense." [Emphasis added]. In the current case, however, the unpredictable effects of making changes to functional groups in molecules which interact with cellular receptors **means that the prior art universe is NOT limited to "a finite number of identified, predictable solutions**," as required for obviousness in *KSR*.

After the *KSR* decision, obviousness with respect to unpredictable arts was further discussed by the U.S. Court of Appeals for the Federal Circuit in *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.* 86 U.S. P.Q. 2d 1196 (Fed. Cir. 2008), wherein the Federal Circuit held that *KSR* "posits a situation with a **finite**, and in the context of the art, **small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness**." [Emphasis added]. In this case, the Federal Circuit goes on to find that, since a person of ordinary skill would not have been likely to start with the lead compound identified in the patent at issue, and would not have had a reason to select a route which produced a specific intermediate from that lead compound, or to stop at that intermediate and test it for activity relating to a different disease state than the original purpose for development, there was "clearly not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Id.* at 1201. The Federal Circuit also disapproved the expert's "obviousness" testimony by saying " Mylan's expert, Dr. Anderson, simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate [the compound in suit] was obvious." *Id.* Accordingly, the Federal Circuit determined that the compound claim is not obvious.

The current application presents a similar situation, in which an array of possible molecules could have been selected as a lead compound, and a nearly infinite number of possible functional group alterations could have been made to any lead compound which had been selected. Furthermore, the effect of any given path could not have been predicted, and could only have been determined after it had been synthesized. Therefore, it is clear that there was not a finite number of identified, predictable solutions for solving the problem addressed in the

instant application, but rather a nearly limitless number of possible options for selecting a lead compound and modifying it, and an entirely unpredictable effect of any given modification.

Applicants therefore respectfully submit that the currently claimed compounds would not have been obvious to one of skill in the art at the time of filing, and request that the rejection of Claims 4, 14, 21, and 24, be withdrawn.

B. The Examiner has rejected Claims 4, 11-14, 21, and 24, under 35 USC 103 over Martinez-Esparza, et al. *Journal of Medicinal Chemistry* 44(3):418-428 (2001). The Examiner states that this reference teaches 1-aryl-3-(4-arylpiperazin-1-yl)propane derivatives, which differ only in that the claimed compounds in the number of carbons in the alkylene linker, and that this would have been an obvious change to one of skill in the art.

As the Examiner has acknowledged, the compound of the cited reference differs from the compounds of Claims 12 and 14 in that the alkylene linker does not have the same number of carbons. Moreover, Claim 4 specifically excludes a compound wherein X=CF_3, n=1, A=N, and Ar is 2-methoxyphenyl, and Claim 11 specifically recites that X=F, whereas the cited reference teaches X=CF_3. Claim 13 has been cancelled.

As described in detail above, the standard for obviousness as determined by the Courts is that the prior art universe relating to the claims be limited to "a finite number of identified, predictable solutions." It has been determined in *Ortho-McNeil* that a prior art universe presenting an array of possible lead compounds, a nearly infinite number of possible functional group alterations, and an inability to predict the effect of a change to any part of the lead compound, does not present a situation which is consistent with a determination of obviousness.

For example, Claim 11 recites X=F, while the reference compound includes X=CF_3. Making the necessary changes to synthesize the compound of the current claims from the reference compound would include: 1) changing an electron withdrawing moiety (CF3) to an

electron donating in a resonance sense, but electron withdrawing in an inductive sense moiety (F); 2) changing a moiety lacking a resonance component (CF_3) for an electron withdrawing moiety in an inductive sense (F); and 3) changing a larger moiety (CF_3) for a smaller moiety (F). Any of these changes would have a different impact on the binding and activity of the molecule at a receptor surface depending on the nature of the particular receptor. Therefore, there would be no way to predict the total effect of so many different and sometimes overlapping changes.

The Examiner cites *In re Henze*, 85 USPQ 261 (1950), which relates to compounds which are homologues of molecules already known in the art. However, *Henze* refers to a different situation for two reasons. First, the compounds recited in Claim 11, as amended, are not homologues in the sense of Henze, which states that a homologue is a molecule which differs from another molecule only by the addition of a CH_2 in a carbon chain (*Id.* at 264). Second, in *Henze*, the alkyl groups in the hydantoin nucleus themselves were thought to be the cause of the narcotic effect (*Id.* at 263), whereas the CH_2 groups in the currently claimed compounds appear to position the critical functional groups, as indicated by the variants. Therefore, *Henze* cannot be considered applicable to this case, and the situation must be reviewed in view of the newer, and more similar decisions presented by *KSR* and *Ortho-McNeil*.

For all of these reasons, Applicants respectfully submit that Claims 4, 11-14, 21, and 24, are not obvious in view of the cited reference, and request that the rejection be withdrawn.

III. Conclusion

Applicants respectfully submit that, in light of the foregoing comments and amendments, all pending claims are now in condition for allowance. A Notice of Allowance is therefore requested.

If any fees are required for filing this substituted amendment, please charge it to Jackson Walker L.L.P. Account No. 10-0096.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,

T. Q. Chwang

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Reg. No. 33,590
Jackson Walker L.L.P.
901 Main Street, Suite 6000
Dallas, Texas 75202
Tel: (214) 953-5959
Fax: (214) 661-6870

January 25, 2010
Date